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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,532	05/25/2001	Beverly L. Davidson	9431-16065	4232

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	09/866,532	DAVIDSON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,11-14 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-7, 11-14, and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed December 2, 2004 (herein after referred to as "the response") has been entered. The after final amendment filed June 17, 2004 was entered as noted in the Advisory Action of July 7, 2004. The amendment filed December 2, 2004 is redundant and does not amend the claims relative to the prior version of the claims. The amendment is improper in using the status identifier "currently amended" for Claims 19-21 because the claims have not been amended relative to the prior version of the claims. The current response does not address or acknowledge the Advisory Action of July 7, 2004.

Claims 1-3, 5-7, 11-14, and 19-21 remain pending.

With regard to the amendments to Claims 19-21, see the Advisory Action of July 7, 2004.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on December 2, 2004 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3, 5, 11, and 12 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in the Office Actions mailed 4/1/03 and 1/12/04 and the Advisory Action mailed 7/7/04, and for further reasons as discussed herein, because the specification, while being enabling for *in vitro* applications of the method, does not reasonably provide enablement for *in vivo* applications of the method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for transducing a cerebellar neuron. The specificaton contemplates using the claimed method *in vivo* for gene therapy applications. The claims encompass both *in vitro* and *in vivo* applications. The specification contemplates using the claimed invention therapeutically to treat a wide variety of CNS disorders as set forth at page 6, line 21 through page 7, line 17. Thus, the only utility asserted for *in vivo* applications of the claimed methods is to produce a therapeutic effect, but the specification fails to adequately teach how to use the claimed methods therapeutically. It is well-established that the specification must teach how to use the claimed method over the full scope. With regard to *in vivo* applications, enablement is evaluated for the sole asserted utility. The only *in vivo* use asserted is for gene therapy.

At page 7, paragraph 1 of the response, Applicants dismiss the cited art of record which demonstrates that the gene therapy art is highly unpredictable, by asserting that "applicants have overcome each of the hurdles described by Rubanyi." However, Rubanyi et al. was published in 2001, after the effective filing date of this application, and is representative of the state of the art at the time of publication. Applicants assert that the specification demonstrates the use of a lentiviral vector to provide efficient expression of the gene contained within the vector in Purkinje cells, because β-galactosidase expression was observed. However, the expression of β-galactosidase does not constitute a therapeutic

effect and the rejection is based on lack of enablement for using the claimed method *in vivo* to produce a therapeutic effect.

At page 7, paragraph 2 of the response, Applicants assert that β-galactosidase is used as a measure of transduction efficiency and is indeed indicative of therapeutic efficacy. Applicants further assert that β-galactosidase is routinely used in the discipline of gene therapy as predictive of whether a particular gene delivery system can provide a therapeutic benefit when used to deliver a therapeutic gene. Contrary to Applicants' belief, β-galactosidase expression is routinely used in the art to test vectors, but is clearly not indicative that a gene delivery system can provide a therapeutic benefit as evidenced by the high level of failure in gene therapy clinical trials which were preceded by successful expression of β-galactosidase in animal studies. As pointed out in the prior Office Actions, the state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al., p. 1789, column 1, paragraph 1). Rather, the prior art shows that intensive investigation has met with limited success.

At page 7, paragraph 3 of the response, Applicants assert that they are providing evidence that β-galactosidase expression is indeed predictive of a therapeutic benefit in the form of several papers and abstracts related to delivery of the lacZ gene to the CNS. Applicants point to Alisky et al. (2000) for demonstrating delivery of the lacZ gene with FIV vectors and concluding that FIV vectors "show promise in correction of cerebellar degeneration both hereditary and acquired." However, the "promise" of being useful in therapeutic protocols does not constitute the **actual** availability or disclosure of even a single therapeutic protocol. Furthermore, a potential for the future use of the vectors in gene therapy does not constitute enablement, but rather is suggestive of a technology that is still undeveloped. One of skill in the art would conclude that the development of gene therapy protocols is not routine if potential successes lie predominantly in the future, not in the past. The references cited in Applicants' response and by the

Examiner provide clear evidence that **intensive effort** has been applied to the development of gene therapy protocols with minimal success.

At page 8, paragraph 1 of the response, Applicants further assert that the FIV delivery system described by Alisky et al. (2000) was used to deliver and express tripeptidyl peptidase I (TPP-I) to Purkinje cells in the mouse CNS. Although not presented as such, Applicants appear to be referring to the publication of Haskell et al. (2003). However, the instant specification does not pertain to the delivery and expression of TPP-I. The instant specification does not contemplate delivering the TPP-I gene. Thus, the post-filing art does not represent evidence that a protocol contemplated and disclosed in the specification was carried out successfully subsequent to filing. Instead, the post-filing art clearly requires numerous further teachings that are not presented in the instant specification. Since the art represents post-filing data, the skilled artisan would not have had the benefit of the teachings of Haskell et al. (2003) at the time of filing. Enablement is evaluated as of the filing date and cannot be supplemented with post-filing teachings to come up with an enabled invention. Furthermore, Haskell et al. (2003) do not disclose a therapeutic effect and only refer to the delivery of TPP-I as a "potential" therapy for LINCL. A **potential** for future success is not representative of an **actual** therapeutic result.

At page 8, paragraph 2 of the response, Applicants point to Stein and Davidson (2002) for stating that "an FIV vector encoding a therapeutic molecule has potential clinical value." However, for the reasons discussed above, a "potential" does not constitute an actual therapeutic result, nor does it demonstrate disclosure of a therapeutic protocol.

At page 8, paragraph 3 of the response, Applicants refer to Brooks et al. (2002). The reference of Brooks et al. (2002, PNAS 99: 6216-6221) has already been considered and is not deemed to evidence enablement of the claimed invention, which is directed to transducing **cerebellar** neurons, not cells of the striatum, cerebral cortex, and hippocampus, as described by Brooks et al. Brooks et al. does not teach treating central nervous system (CNS) disorders by transducing cerebellar neurons. The instant

specification does not provide specific guidance for expressing β-glucuronidase at therapeutic levels in the striatum, cerebral cortex, or hippocampus as described by Brooks et al. Since this reference is post-filing art, one of skill in the art would not have had the benefit of the teachings of Brooks et al. (2002) and therefore would not have been able to develop a therapeutic protocol for the treatment of lysosomal storage disease without undue experimentation. The limited teachings of the specification would not have led one of skill in the art to develop the protocol described by Brooks et al. Rather the instant method is directed to providing therapeutic expression within **cerebellar** neurons. Thus, Applicants' arguments are not commensurate in scope with the scope of the claims. Applicants argue that the methods of Brooks et al. are analogous to the methods taught in the instant specification and therefore "provides credible evidence that gene delivery methods as described in the present application can provide a therapeutic benefit and that β-galactosidase is predictive of this benefit." The Examiner does not agree because the method used by Brooks et al. is directed to transducing different cell types from those recited in the instant claims, and further is directed to providing β-glucuronidase for the treatment of lysosomal storage disease, methodology not taught in the instant specification. Given the state of the art for gene therapy, undue experimentation, rather than routine experimentation was required to achieve the result reported by Brooks et al. Neither Brooks et al. nor the instant specification provides enabling guidance teaching one of skill in the art how to produce a therapeutic effect or prevent a CNS disorder by transducing cerebellar neurons using a lentiviral vector. Furthermore, given the state of the art of gene therapy, where constructs must be designed on a case by case basis and therapeutic protocols are developed by painstaking intensive research, the result reported by Brooks et al. would not be considered enabling by one skilled in the art for the broad scope of treating all CNS disorders. The instant claims are directed to treating and preventing any central nervous system disorder and the specification refers to a wide variety of CNS disorders that will be treated or prevented using the claimed method. Thus, Applicants' arguments are not commensurate in scope with the scope of the claims.

At page 9, paragraph 3 of the response, Applicants point to an abstract of Hagihara et al. (2000) for stating that "the infusion of HVJ-AVE liposomes into the cerebrospinal fluid (CSF) space is applicable for widespread gene delivery into the CNS of large animals." Nevertheless, gene delivery is not gene therapy. There is nothing in the reference that correlates β-galactosidase gene expression to a therapeutic effect.

At page 9, paragraph 3 of the response, Applicants point to an abstract of Agudo et al. (2002) for demonstrating lacZ gene expression in Purkinje cells by administration of an HSV-1 amplicon vector and suggesting the "possibility of using these vectors for long-term gene therapy of human cerebellar disorders." Again, a "possibility" does not constitute an actual correlation between β-galactosidase gene expression to a therapeutic effect.

At page 10, paragraph 1 of the response, Applicants point to Kyrkanides et al. (2003) for demonstrating successful delivery and expression of the lacZ gene in Purkinje cells using an FIV vector. However, the enablement rejection is based on lack of enablement for using the delivery method to produce a therapeutic effect in a variety of brain disorders. Since Kyrkanides et al. does not disclose production of a therapeutic effect, it does not pertain to the enablement rejection, as it does not address the obstacles remaining to the development of therapeutic protocols once a gene delivery method is provided.

At page 10, paragraph 2 of the response, Applicants assert that art recognized screening procedures and tests can be relied on to establish utility under 35 U.S.C. 112, first paragraph. Applicants point to *In re Brana* (CAFC 1995) for addressing pharmaceutical inventions. In *Brana* the court found that the disclosed activity for the claimed compounds was sufficient to demonstrate their utility. Contrary to the situation here, in *Brana* the claims were directed to compounds, not treatment claims as is the case here. Here, the issue is whether the specification provides an enabling disclosure for producing a therapeutic effect across a wide variety of brain diseases and disorders based solely on disclosure of a

gene delivery method. Contrary to *Brana*, the instant specification does not demonstrate a therapeutic effect upon lentiviral vector-mediated gene delivery. Also in contrast to Brana, the instant invention relates to an art that is highly unpredictable and subject to known difficulties in taking gene delivery methods and developing therapeutic protocols using that particular form of gene delivery.. In *Brana*, other very similar compounds were known in their art and their pharmaceutical uses were already established.

At page 10, paragraph 3 of the response, Applicants state that Alisky demonstrated a therapeutic benefit upon expression of TPP-I in Purkinje cells. Contrary to Applicants statement, the two references cited in this response where Alisky is an author do not disclose a therapeutic effect.

None of the references cited demonstrate that β-galactosidase gene expression is predictive of a therapeutic effect.

Thus, the rejection is maintained for reasons of record.

Claims 6, 7, 13, 14, and 19-21 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record advanced in the Office Actions mailed 4/1/03, 1/12/04, and 7/7/04. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for transducing a cerebellar neuron *in vivo* or *ex vivo*, a method of treating or preventing cerebellar neuronal degeneration, and a method of treating or preventing a central nervous system disorder. The claims are exclusively directed to *in vivo* methods and *ex vivo* protocols that require administration of a neuron to a subject. These claims do not encompass *in vitro* applications.

These claims remain rejected for reasons of record and for the reasons discussed herein above. For the reasons discussed above and reasons of record, the specification fails to provide an enabling disclosure for therapeutic protocols.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 6, 19, and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Bosch et al. (May 20, 2000, Human Gene Therapy 11: 1139-1150).

Bosch et al. (2000) disclose the use of an HIV-1 vector for gene delivery to the cerebellum in an animal model of lysosomal storage disease. An HIV-1 vector encoding β-glucuronidase was introduced into several regions of the brain including the cerebellum. The vector contains the human β-glucuronidase cDNA downstream of the cytomegalovirus (CMV) enhancer and promoter elements and HIV LTRs (page 1140, column 2, paragraph 2). The vector comprises the vesicular stomatitis virus envelope G protein (VSV-G) which thus provides a lentiviral vector that preferentially infects neurons over other cell types (see page 1140, column 1, paragraph 2 and column 2, paragraph 2). The vector genome was readily detected in the cerebellum (see Figure 5) and correction of lysosomal storage lesions was observed throughout the entire brain (see Figure 6).

Thus, the claimed invention is disclosed in the prior art.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Mochizuki et al. (1998).

Mochizuki et al. (1998) disclose the use of an HIV-1 vector for gene delivery into cerebellar neurons. The reference discloses that the vector constructs contain a reporter gene and *cis*-acting sequences required for packaging, reverse transcription, and integration, including 5′ and 3′ LTRs (page 8875, column 2, paragraph 3).

Thus, the claimed invention is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poeschla et al. (1998), Dow et al. (1990), and Cummings et al. (1998).

Poeschla et al. (1998) disclose the efficient transduction of nondividing human cells by an FIV vector. The FIV vector is shown in Figure 1 and comprises the 5′ LTR, the tRNA binding site, a packaging signal, a CMV promoter operably linked to a lacZ gene, the origin of second strand DNA synthesis, and the 3′ LTR. The reference does not disclose the use of the vector to transduce cerebellar neurons. However, it clearly discloses that the vector does transduce nondividing cells.

Dow et al. (1990) disclose that the feline immunodeficiency virus (FIV) infects the cerebellum. The authors demonstrate and conclude that FIV is a neurotropic lentivirus.

Cummings et al. (1998) disclose that spinocerebellar ataxia type 1 (SCA1) is a neurodegenerative disease that affects the Purkinje cells of the cerebellum. The disease is characterized by progressive

motor deterioration and loss of cerebellar Purkinje cells. The reference further discloses a transgenic mouse model of SCA1, where the mice express a mutant form of ataxin-1. Chaperone overexpression reduces the pathological ataxin-1 aggregates observed in HeLa cells (page 153, column 1, paragraph 2). The authors point out that it is desirable to introduce various Hsp genes into the Purkinje cells of the SCA1 transgenic mouse (page 153, column 1, paragraph 3).

In view of the art-recognized need for delivering genes to cerebellar neurons, the skilled artisan would have used an FIV vector such as the one disclosed by Poeschla et al. and modified it to include a gene of interest, such as a gene encoding a chaperone protein, instead of the lacZ reporter gene, particularly in view of the teachings in the art, which disclose that FIV vectors will transduce cerebellar cells, as taught by Dow et al., and that FIV vectors efficiently transduce nondividing cells, as taught by Poeschla et al. The skilled artisan would have further been motivated to introduce an FIV vector encoding a chaperone into the cerebellum of SCA1 transgenic mice to determine the effect of chaperone expression on ataxin-1 aggregation.

One of skill in the art would have been motivated to combine the teachings of Poeschla et al., Dow et al., and Cummings et al. in order to express a protein of interest in the cerebellum of an animal in need of treatment of a disease that causes cerebellar degeneration.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1-3, 5-7, and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curran et al. (2000), Dow et al. (1990), and Cummings et al. (1998).

Curran et al. (2000) disclose the efficient transduction of nondividing cells by optimized FIV vectors. A number of different vector constructs are disclosed in Figure 1. The pFLX-W5L, for example, comprises the 5′ LTR, the tRNA binding site, a packaging signal, a PGK promoter operably linked to a

lacZ gene, the origin of second strand DNA synthesis, and the 3' LTR. Some of the vector constructs were made by replacing the viral U3 region with a stronger promoter. The reference does not disclose the use of the vector to transduce cerebellar neurons. However, it clearly discloses that the vector efficiently transduces nondividing cells.

Dow et al. (1990) disclose that the feline immunodeficiency virus (FIV) infects the cerebellum. The authors demonstrate and conclude that FIV is a neurotropic lentivirus.

Cummings et al. (1998) disclose that spinocerebellar ataxia type 1 (SCA1) is a neurodegenerative disease that affects the Purkinje cells of the cerebellum. The disease is characterized by progressive motor deterioration and loss of cerebellar Purkinje cells. The reference further discloses a transgenic mouse model of SCA1, where the mice express a mutant form of ataxin-1. Chaperone overexpression reduces the pathological ataxin-1 aggregates observed in HeLa cells (page 153, column 1, paragraph 2). The authors point out that it is desirable to introduce various Hsp genes into the Purkinje cells of the SCA1 transgenic mouse (page 153, column 1, paragraph 3).

In view of the art-recognized need for delivering genes to cerebellar neurons, the skilled artisan would have used an FIV vector such as the one disclosed by Curran et al. and modified it to include a gene of interest, such as a gene encoding a chaperone protein, instead of the lacZ reporter gene, particularly in view of the teachings in the art, which disclose that FIV vectors will transduce cerebellar cells, as taught by Dow et al., and that FIV vectors efficiently transduce nondividing cells, as taught by Curran et al. The skilled artisan would have further been motivated to introduce an FIV vector encoding a chaperone into the cerebellum of SCA1 transgenic mice, based on the teachings of Cummings et al., to determine the effect of chaperone expression on ataxin-1 aggregation.

One of skill in the art would have been motivated to combine the teachings of Curran et al., Dow et al., and Cummings et al. in order to express a protein of interest in the cerebellum of an animal in need of treatment of a disease that causes cerebellar degeneration.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER